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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 487/08, A61K 31/395, C07D 471/08

A1

(11) International Publication Number: WO 93/15080

(43) International Publication Date: 5 August 1993 (05.08.93)

(21) International Application Number: PCT/GB93/00174

(22) International Filing Date: 27 January 1993 (27.01.93)

(30) Priority data:
9201751.6 28 January 1992 (28.01.92) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

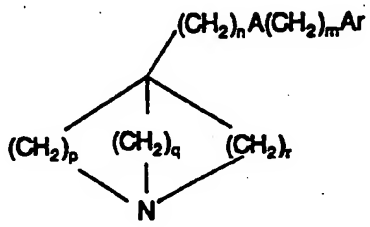
(75) Inventors/Applicants *(for US only)* : ORLEK, Barry, Sidney [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). BROWN, Thomas, Henry [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The pinnacles, Harlow, Essex CM19 5AD (GB). COOPER, David, Gwyn [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).

(74) Agent: FLORENCE, Julia, A.; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AZABICYCLO COMPOUNDS AS CALCIUM CHANNEL ANTAGONISTS



(I)

(57) Abstract

Compounds of formula (I) in which p, q and r each independently represent an integer from 1 to 4; n is 0 to 6; m is 0 to 6; A is a bond, -CH=CH-, -C≡C-, oxygen, sulphur or NR^1; R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl; and Ar is aryl or heteroaryl, each of which may be optionally substituted; and salts thereof are useful in medicine, in particular as calcium channel antagonists. Processes for preparing compounds (I) and pharmaceutical compositions containing them are also described.

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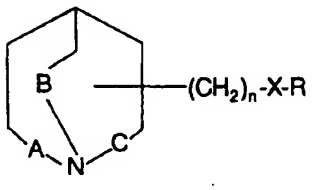
Azabicyclo compounds as calcium channel antagonists

The present invention relates to novel azabicyclic derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, in particular as calcium channel antagonists.

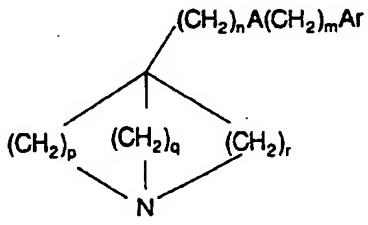
German OLS 41 16582 describes azabicyclic compounds of the formula :



wherein A, B and C independently represent -CH_2- or a single bond; n is zero, 1 or 2; X is oxygen or sulphur and R is inter alia phenylalkyl, diphenylalkyl, heterocyclicalkyl, phenyl, diphenyl or a heterocycle, each of which may be optionally substituted. These compounds are said to be useful as muscarinic agonists.

We have now found novel azabicyclic compounds, substitued at the bridgehead carbon atom, which have activity as calcium channel antagonists.

In a first aspect, the present invention provides, a compound of formula (I):



Formula (I)

in which

p, q and r each independently represent an integer from 1 to 4;
n is 0 to 6;
m is 0 to 6;

A is a bond, -CH=CH-, -C≡C-, oxygen, sulphur or NR^1;
R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl; and
Ar is aryl or heteroaryl, each of which may be optionally substituted;

and salts thereof.

p and r are preferably 2 or 3.

q is preferably 1 or 2.

The values of n, m and A should be chosen such that the length of the chain $-(CH_2)_nA(CH_2)_m$ is at least two atoms. In general the length of the chain $-(CH_2)_nA(CH_2)_m$ is from 2 to 6 e.g. 2 to 5 atoms. Preferred values for n and m depend on the group A. Thus for example, when A is oxygen the sum of n+m is from 1 to 5, for example n may be zero, 1 or 2 and m may be zero or 1 to 5.

A is preferably oxygen or a bond, most preferably oxygen.

When Ar represents aryl, suitable groups include, for example, unsaturated monocyclic and unsaturated or partially saturated bicyclic or tricyclic ring systems of up to 15 carbon atoms, such as, for example, phenyl, naphthyl, tetrahydronaphthyl, fluorene, fluorenone, dibenzosuberene and dibenzosuberenone . Preferred are optionally substituted phenyl rings.

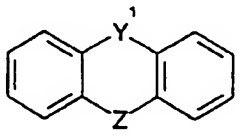
An aryl group may be substituted, for example, by a C_{1-2}alkylenedioxy group (e.g. phenyl substituted by a 3,4-methylenedioxy group) or by 1 to 3 substituents selected from halogen, C_{1-4}alkoxy, nitro, SC_{1-4}alkyl, $NR^{2a}R^{2b}$ (in which R^{2a} and R^{2b} can be independently H or C_{1-4}alkyl), OCF_3, C_{1-6}alkyl, trifluoromethyl, CN, optionally substituted phenyl, optionally substituted phenoxy, optionally substituted phenylC_{1-4}alkyl and optionally substituted phenylC_{1-4}alkoxy.

Suitable optionally substituted phenylC_{1-4}alkyl groups include, for example benzyl. Suitable optionally substituted phenylC_{1-4}alkoxy groups include, for example benzyloxy groups.

Suitable substituents for said optionally substituted phenyl, phenoxy, phenylC_{1-4}alkyl and phenylC_{1-4}alkoxy groups include for example halogen, C_{1-4}alkyl, C_{1-4}alkoxy, nitro and trifluoromethyl groups.

Preferably the aryl group Ar is a phenyl ring substituted by one or two substituents, in particular, by a phenyl, phenyl(C_{1-4})alkyl e.g. benzyl, phenoxy or phenylC_{1-4}alkoxy, e.g. benzyloxy group; or by two chloro atoms especially in the 3- and 4-positions of the phenyl ring.

When Ar represents heteroaryl suitable groups include, for example, unsaturated or partially saturated bicyclic and tricyclic ring systems containing at least one heteroatom. A bicyclic ring system preferably contains 8 to 10 ring members, such as quinolinyl, tetrahydroquinolinyl or benzofuranyl. A tricyclic ring system preferably contains from 11 to 15 ring members, and most preferably has the structure :



wherein Y^1 represents $Y(CH_2)_t$, Y is O, S or NR^3 (where R^3 is hydrogen or C_{1-4}alkyl), Z is $(CH_2)_s$ or -CH=CH-, s is 0, 1 or 2 and t is 0 or 1 or is a corresponding dehydro ring system. Examples of tricyclic heteroaryl groups include dibenzofuranyl, dibenzothienyl, carbazole, N-methylcarbazole, acridine and dibenzoxepine . The heteroaryl ring can be linked to the remainder of formula (I) via any suitable ring atom.

Suitable substituents for said heteroaryl rings include, for example, 1 to 3 substituents selected from halogen, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, phenylC_{1-4}alkyl, and phenylC_{1-4}alkoxy.

Alkyl groups present in the compounds of formula (I), alone or as part of another group, can be straight or branched. Thus a C_{1-4}alkyl group may be for example methyl, ethyl, n-propyl, n-butyl or any branched isomer thereof such as isopropyl or t-butyl.

It will be appreciated that for use in medicine a salt of a compound (I) should be pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, methanesulphonate or similar pharmaceutically acceptable inorganic or organic acid addition salts. Other non-pharmaceutically acceptable salts may be used for example in the isolation of the final product and are included within the scope of this invention.

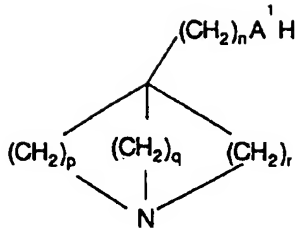
Particular compounds of the invention include:

4-[2-(3,4-dichlorophenoxy)ethyl]-1-azabicyclo[2.2.1]heptane hydrochloride,
4-[2-(4-benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.1]heptane hydrochloride,
4-[2-(2-dibenzofuranyloxy)ethyl]-1-azabicyclo[2.2.1]heptane hydrochloride,
(±)5-(4-benzyloxyphenoxymethyl)-1-azabicyclo[3.2.1]octane hydrochloride,
(±)5-(4-benzylphenoxymethyl)-1-azabicyclo[3.2.1]octane hydrochloride,
(±)5-(2-dibenzofuranyloxy)methyl-1-azabicyclo[3.2.1]octane hydrochloride,
(±) 5-[2-(2-dibenzofuranyloxy)ethyl]-1-azabicyclo[3.2.1]octane hydrochloride,
4-[2-(4-phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.1]heptane hydrochloride,
4-[3-(4-benzyloxyphenyl)propyloxymethyl]-1-azabicylo[2.2.1]heptane hydrochloride,
4-[5-(4-phenoxyphenyl)pentyloxy]-1-azabicyclo[2.2.1]heptane hydrochloride,
4-(4-benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride,
4-[4-(4-phenoxyphenyl)butyloxy]-1-azabicyclo[2.2.1]heptane hydrochloride,
4-[3-(4-benzyloxyphenyl)propyloxy]-1-azabicyclo[2.2.1]heptane hydrochloride, and
4-[5-(4-benzyloxyphenyl)pentyloxy]-1-azabicyclo[2.2.1]heptane hydrochloride.

It will be appreciated that certain compounds of formula (I) may contain one or more asymmetric centres, for example where p, q and r all have different values. Such compounds will exist as optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention. In addition, when A represents -CH=CH- the compounds will exist as geometric isomers, and the invention encompasses all such isomers and mixtures thereof.

The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides in a further aspect, a process for the preparation of a compound of formula (I) which comprises:

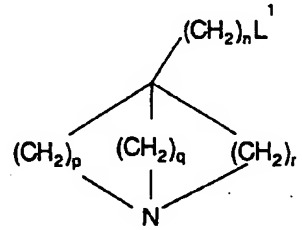
(a) for compounds of formula (I) in which A is O, S or NR^1, reaction of a compound of formula (II):



Formula (II)

in which p, q, r and n are as described for formula (I) and A^1 is O, S or NR^1, with a compound of formula $L(CH_2)_mAr$ in which m and Ar are as described for formula (I), and L is a leaving group;

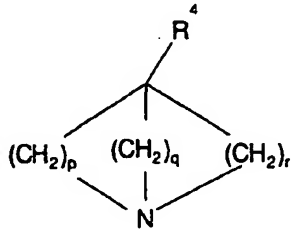
(b) for compounds of formula (I) in which A is O, S or NR^1, reaction of a compound of formula (III):



Formula (III)

in which p, q, r and n are as described for formula (I) and L^1 is a group displaceable by a nucleophile, with a compound of formula $HA^1(CH_2)_mAr$ where m and Ar are as described for formula (I) and A^1 is as described for formula (II); or

(c) for compounds of formula (I) in which A is NR^1, reduction of a compound of formula (IV) :



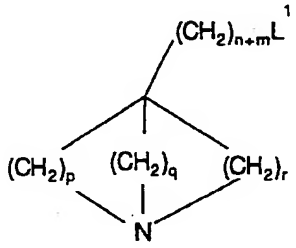
Formula (IV)

in which R^4 represents the group

$-(CH_2)_nN(R^1)C(O)(CH_2)_{m-1}Ar$ or $-(CH_2)_{n-1}C(O)N(R^1)(CH_2)_mAr$,

and p, q, r, n, m, and Ar are as described for formula (I);

(d) for compounds of formula (I) in which A is a bond, reaction of a compound of formula (V) :

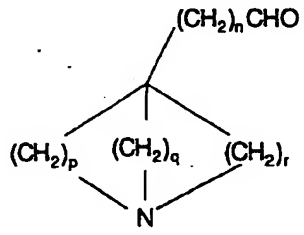


Formula (V)

(wherein L^1, p, q, r, m and n are as hereinbefore defined).

with a compound of formula X^1Ar in which Ar is as described for formula (I), and X^1 is an alkali metal;

(e) For compounds wherein A is -CH=CH- reaction of a compound of formula (VI) :



Formula (VI)

(wherein n, p, q and r are as hereinbefore defined) with a reagent serving to introduce the group Ar;

(f) Interconversion of one compound of formula (I) to a different compound of formula (I) e.g. the reduction of a compound wherein A is -CH=CH- to a compound wherein A is $-CH_2CH_2-$;
and optionally thereafter forming a salt.

In process (a) the reaction between a compound of formula (II) and a compound $L(CH_2)_mAr$ can take place under conditions which depend on the nature of the group L and the value of m. For example, when L is halogen or a sulphonic acid residue such as a tosylate or mesylate and m is other than zero, the reaction is carried out under standard conditions in a solvent, optionally in the presence of a base. When a fluoro-substituted aryl compound F-Ar is employed in process (a), (to prepare compounds where m is zero) the reaction is effected in the presence of a strong base such as sodium hydride, and in an inert organic solvent such as dimethylformamide. Preferably the aryl group is substituted by an activating group such as CF_3 or NO_2. If necesary, the azabicyclic nitrogen atom may be protected during the reaction by methods well known in the art, e.g. by prior formation of a quaternary derivative such as an N-benzyl derivative. Protection may also be effected by formation of a borane (BH_3) complex. It will be appreciated that the N-protecting group should be chosen such that it can be removed without affecting other moieties in the molecule. Thus for example a benzyl protecting group may not be appropriate when the side chain $(CH_2)_nA(CH_2)_mAr$ also contains a benzyl moiety such as a benzyloxy group. In general, N-protection is preferred when the leaving group L represents halogen, e.g. bromine, but when L is a sulphonic acid residue e.g. a tosylate, N-protection may not be necessary.

The reaction between a compound of formula (III) and a compound of formula $HA^1(CH_2)_mAr$ (process (b)) can take place under conditions which depend on the nature of L^1 and A. For example when L^1 is hydroxy, m is 0 and A^1 is oxygen or sulphur the reaction is carried out in the presence of diethyl azodicarboxylate and triphenyl phosphine. Such a reaction is known as the Mitsunobu reaction (as described in Synthesis 1981, 1). Alternatively the leaving group L^1 may be for example a halogen atom or a sulphonyloxy group eg. methane-sulphonyloxy or p-toluene sulphonyloxy in which case the compound (III) may preferably be protected, e.g. as an acid salt such as a hydrochloride salt. Reaction may be effected in the presence or absence of solvent, at a temperature in the range 0 to 200°C, and may preferably be carried out in the presence of a base.

The reduction of a compound of formula (IV) according to process (c) can be effected by methods known in the art, for example using a reducing agent such as lithium aluminium hydride. Conveniently a compound of formula (IV) can be prepared (for example as

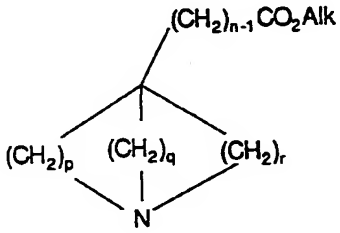
described below) and reduced in a 'one-pot' reaction, without isolation of compound (IV) itself.

The reaction between a compound of formula (V) and a compound of formula X^1Ar in process (d) can take place under standard conditions known to those skilled in the art for the formation of carbon-carbon bonds.

Process (e) may be effected using a Wadsworth-Emmons reagent for example of the formula $Ar(CH_2)_{m+1}P(O)(OAlk)_2$, such as a diethylphosphonate, or a Wittig reagent of the formula $Ar(CH_2)_{m+1}PPh_3X$ (where X is an anion) which compounds are available commercially or can be prepared by known methods. The reaction may be carried out in a solvent such as tetrahydrofuran, optionally containing a crown ether such as 15-crown-5, or 18-crown-6, and in the presence of a strong base such as sodium hydride, or potassium t-butoxide.

Interconversion reactions according to process (f) may be effected by methods well known in the art. Thus for example conversion of a compound (I) wherein A represents -CH=CH- into a compound (I) wherein A represents-CH_2-CH_2- may be effected by catalytic reduction.

Compounds of formula (II) wherein n is 1-6 and A^1 is oxygen can be prepared by reduction of the corresponding ester of formula (VII) :



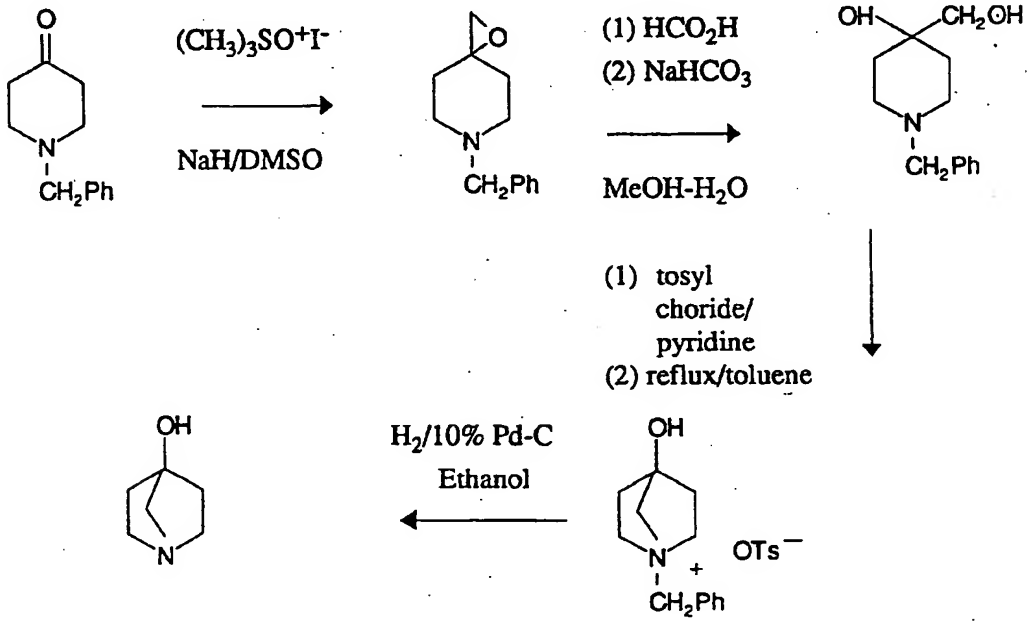
Formula (VII)

wherein p, q and r are as hereinbefore defined and Alk is a C_{1-6}alkyl group e.g. ethyl. The reduction may be effected using a reducing agent such as lithium aluminium hydride in a solvent such as diethyl ether or tetrahydrofuran. Esters of formula (VII) wherein n is 1 are described for example in European Patent Applications 287356 and 392803 and by Eckhardt et al Helv. Chim Acta, 1972, 55, 2432, and B.S. Orlek et al., J. Med. Chem., 1991, 34, 2726. Esters wherein n is greater than 1 may be prepared by conversion of an ester wherein n is 1 to the corresponding N-methyl-N-methoxycarboxamide (e.g. by

hydrolysis of the ester followed by reaction with thionyl chloride and N,O-dimethylhydroxylamine hydrochloride), which is then reduced to the aldehyde using diisobutylaluminium hydride. The aldehyde is further converted to the cyanomethyl derivative for example as described in EPA 363085, followed by acid hydrolysis, and esterification to form an ester wherein n is 2. The sequence may be repeated to form higher homologues.

Alternatively compounds of formula (II) may be prepared by reaction of an aldehyde of formula (VI) with triethylphosphonoacetate or triethylphosphonocrotonate, followed by catalytic hydrogenation to give an ethoxycarbonylalkyl derivative which is further reduced e.g. using lithium aluminium hydride, to the desired hydroxyalkyl compound. It will be appreciated that use of triethylphosphonoacetate results in a 2-carbon homologation whilst triethylphosphonocrotonate gives a 4-carbon homologation.

Compounds of formula (II) wherein n is zero and p and r are both 2 may be prepared from 1-benzyl-4-piperidone, by a variety of methods. For example, a compound (II) wherein r is 1 may be prepared according to the following reaction scheme :



Alternatively the 1-benzyl-4-piperidone may be converted to the 4-hydroxy-4-hydroxymethyl compound by the method described in EPA 188255, via corresponding cyano and ester derivatives.

A compound of formula (II) wherein n is zero, and p, q and r are each 2 may be prepared by the method of C.A. Grob and P. Brenneisen (Helv. Chim. Acta., 41, 1184, 1958) in which 1-benzyl-4-piperidone is reacted with zinc and ethylbromoacetate to give the corresponding 1-hydroxy-1-ethoxycarbonylmethyl derivative which is reduced using lithium aluminium hydride to the 1-hydroxy-1-hydroxyethyl compound and then treated as above to effect cyclisation and deprotection.

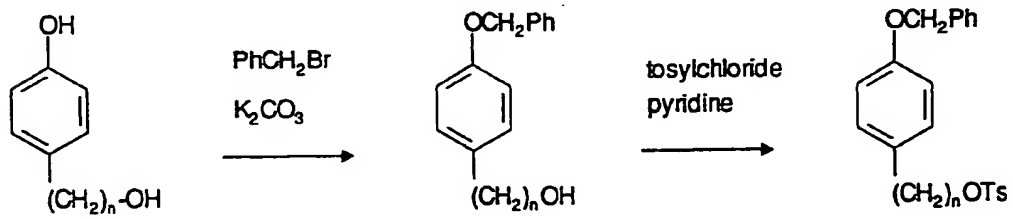
Compounds of formula (II) wherein n is zero, p is 3, r is 2 and q is 1, may be prepared as described in EPA 287356.

Compounds of formula (II) wherein A^1 is S or NR^1 may be prepared from the corresponding hydroxy compound by standard methods, for example via formation of an alkyl halide followed by reaction with an appropriate amine or thiol.

Compounds of formula (III) wherein L^1 is OH can be prepared as described for compounds of formula (II), and compounds of formula (III) wherein L^1 is a halogen atom, or a mesyloxy or tosyloxy group can be prepared from the corresponding alcohol in conventional manner.

The compounds of formula $L(CH_2)_mAr$ and $HA^1(CH_2)_mAr$ may be prepared by standard methods well known in the art. For example compounds $L(CH_2)_mAr$ wherein Ar is a substituted phenyl group and L is halo, e.g. bromo, may be prepared by Friedel-Crafts acylation of the corresponding substituted benzene derivative, using an appropriate acid chloride and catalysed by aluminium trichloride, followed by reduction in situ with triethylsilane.

When Ar represents a phenyl group substitued by benzyloxy compounds $L(CH_2)_mAr$ may be prepared according to the following scheme :



The starting materials are available commercially or may be prepared by standard methods, e.g. by reaction of 4-benzyloxybenzaldehyde with triethylphosphonocrotonate in a similar manner to that described for the preparation of compounds (II).

Compounds of formula (IV) wherein R^4 is a group $-(CH_2)_nN(R^1)C(O)(CH_2)_{m-1}Ar$ can be prepared by reacting a compound of formula (II) wherein A^1 represents NR^1 with an acylating agent corresponding to the group $-(CH_2)_mAr$, for example an acid chloride $ClOC(CH_2)_{m-1}Ar$.

Compounds of formula (IV) wherein R^4 is a group $-(CH_2)_{n-1}C(O)N(R^1)(CH_2)_mAr$ may be prepared for example by reaction of a corresponding compound wherein R^4 represents $-(CH_2)_{n-1}CO_2H$ or an activated derivative thereof such as an acid halide, ester or anhydride, with an amine of formula $HN(R^1)(CH_2)_m$ Ar. It will be appreciated that when the acid itself is employed, reaction with the amine should be effected in the presence of a coupling agent. The carboxylic acid may itself be prepared for example by oxidation of the corresponding alcohol, ie. a compound of formula (II) wherein A^1 is oxygen.

Compounds of formula (V) may be prepared in analogous manner to compounds of formula (III); where necessary the chain length may be increased using methods well known in the art.

Compounds of formula (VI) may be prepared by conventional methods, for example the oxidation of a compound of formula (II) wherein A^1 is oxygen, or conversion of the corresponding ester, e.g. via the corresponding N-methyl-N-methoxycarboxamide and reduction with diisobutylaluminium hydride, as described hereinabove. Compounds of formula (VI) wherein n is 1 may be prepared from the corresponding compound wherein n is zero by various methods. For example the aldehyde wherein n is zero may be treated with (methoxymethyl) triphenylphosphonium chloride and potassium t-butoxide, followed by a strong acid, e.g. concentrated sulphuric acid, resulting in the aldehyde wherein n is 1. Alternatively the aldehyde may be converted to the corresponding cyanomethyl derivative as described in EPA 363085 followed by acid hydrolysis, conversion to the N-methyl-N-methoxycarboxamide and reduction. These procedures may also be used to form higher homologues.

When a compound of formula (I) is obtained as a mixture of enantiomers, these may be separated by conventional methods such as crystallisation in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column.

The compounds of the invention have been found to exhibit high calcium influx blocking activity for example in neuronal cells. As such the compounds are expected to be of use in

therapy in treating conditions and diseases related to an accumulation of calcium in the brain cells of mammals, in particular humans. For example, the compounds are expected to be of use in the treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal.

In a further aspect of the invention there is therefore provided a method of treatment of conditions or diseases related to (e.g. caused or exacerbated by) the accumulation of calcium in the brain cells of mammals (e.g. humans) which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Thus for example, the present invention provides a method of treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal, which comprises administering to a subject in need thereof, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a yet further aspect the invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition or a disease related to (e.g. caused or exacerbated by) the accumulation of calcium in the brain cells of a mammal (e.g. a human).

For use in medicine, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

The compounds of the invention may be administered by any convenient method, for example by oral, parenteral, buccal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compounds of the invention may also be administered parenterally, by bolus injection or continuous infusion. Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Both liquid and solid compositions may contain other excipients known in the pharmaceutical art, such as cyclodextrins.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 60 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, eg. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 60 mg, eg. 1 to 40 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Alternatively the compounds of the invention

may be administered by continuous intravenous infusion, preferably at a dose of up to 400 mg per day. Thus the total daily dosage by oral administration will be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

Ca^{2+} Current Measurement

Cell preparations

Sensory neurons from dorsal root ganglia were dissociated from 1 day old rat pups (Forda et al, Developmental Brain Research, 22 (1985), 55-65). Cells were plated out onto glass coverslips and used within 3 days to permit effective voltage clamp of Ca^{2+} currents.

Solutions

The pipette (internal solution) contained in mM: CsCl, 130; HEPES, 10; EGTA, 10; $MgCL^2$, 4; ATP, 2; buffered to pH 7.2 with CsOH. Cells were bathed in a normal Tyrodes solution before establishment of whole cell recording when the bathing solution was changed to one allowing isolation of Ca^{2+} currents. The external solution for recording Ca^{2+} channel currents contained in mM: $BaCL^2$, 10; TEA-Cl, 130; glucose, 10; HEPES, 10; $MgCL^2$, 1; buffered to pH 7.3 with TEA-OH. Barium was used as the charge carrier as this assists in current isolation and calcium dependent inactivation of current is avoided. Compounds were dissolved in DMSO to make a 20 mM stock solution. At the drug concentration used the vehicle (0.1%) had no significant effect on Ca^{2+} currents. All experiments were performed at 21 to 24°C. Whole cell currents were recorded using List EPC-7 amplifiers and stored, digitised for later analysis using PC based software similar to that described previously (Benham & Tsien, Journal of Physiology (1988), **404**, 767-784).

Ca^{2+} currents

Peak voltage gated Ca^{2+} channel currents of up to 10 nA from dorsal root ganglion neurons were recorded using 10 mM Ba^{2+} as charge carrier. Currents were evoked from a holding potential of -80 mV to a test potential of 0 or +10 mV every 15 seconds. This test potential was at the peak of the current voltage relationship and assessing block at this point reduced any errors due to drifting holding potential. Some cells showed slow rundown of current as is commonly seen when recording Ca^{2+} currents. The rundown rate was measured in control conditions and extrapolated through the time of drug

application to derive a control value to relate the drug affected current to. Block by 20 μM drug was assessed 3 minutes after drug application.

Compounds of the invention gave percentage inhibition of plateau Ca^{2+} current in the range 71 to 99%.

PHARMACEUTICAL FORMULATIONS

1. Formulation for intravenous infusion

Compound of formula (I)	0.1 - 60 mg
Sodium hydroxide/hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 30 ml
propylene glycol	0 - 30 ml
alcohol	0 - 10 ml
water	to 100 ml

2. Formulation for bolus injection

Compound of formula (I)	0.1 - 60 mg
sodium hydroxide or hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 2.5 ml
alcohol	0 - 2.5 ml
water	to 5 ml

A tonicity adjusting agent eg. sodium chloride, dextrose or mannitol may also be added.

3. Tablet for oral administration

	mg/tablet
Compound of formula (I)	25
lactose	153
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	255

The following non-limiting examples illustrate the preparation of compounds of formula (I)

Preparation 1

4-(Methoxycarbonylmethyl)-1-azabicyclo[2.2.1]heptane

A solution of 4-(cyanomethyl)-1-azabicyclo[2.2.1]heptane (EP 363085, Description 25) (1.94g, 14.3mmol) in 5N hydrochloric acid (25ml) was heated under reflux for 12h. The reaction mixture was concentrated *in vacuo*, then coevaporated with toluene to remove the last traces of water. The residue was dissolved in methanol (50ml), treated with 1M ethereal hydrogen chloride then heated at reflux for 2h. The solution was concentrated *in vacuo*, treated with aqueous potassium carbonate (25ml) and extracted into chloroform (3x25ml). The combined organic extracts were dried over sodium sulphate, concentrated *in vacuo* and the oil produced was distilled to afford the **title compound** as a clear oil (2.1g, 87%) b.p. 125°C, 0.4mm Hg (Kugelröhr).

^{1}H Nmr ($CDCl_3$) δ: 1.28-1.42 (2H, m), 1.49-1.64 (2H, m), 2.37 (2H, s), 2.52-2.71 (4H, m), 2.87-3.02 (2H, m), 3.67 (3H, s).

Preparation 2

4-(2-Hydroxyethyl)-1-azabicyclo[2.2.1]heptane

A solution of 4-(methoxycarbonylmethyl)-1-azabicyclo[2.2.1]heptane (2.1g, 12.4mmol) in dry diethyl ether (10ml) was added to a stirred suspension of lithium aluminium hydride (0.94g, 24.9mmol) in dry diethyl ether (70ml), under nitrogen. The reaction was stirred at room temperature for 2.5h and then quenched by careful addition of the minimum amount of water. The reaction was filtered and the precipitate washed thoroughly with 20% methanol in diethyl ether. The combined filtrate and washings were concentrated *in vacuo* and the residue was distilled to afford the **title compound** as a white solid (1.49g, 85%) b.p. 155°C, 0.3mm Hg (Kugelröhr).

^{1}H Nmr ($CDCl_3$) δ: 1.20-1.35 (2H, m), 1.42-1.57 (2H, m), 1.94 (2H, t, J=7Hz), 2.29 (2H, m), 2.39-2.80 (3H, m), 2.84-3.00 (2H, m), 3.72 (2H, t, J=7Hz).

Preparation 3
(±)5-Hydroxymethyl-1-azabicyclo[3.2.1]octane

The title compound was prepared in a similar manner to Preparation 2 from (±)ethyl 1-azabicyclo[3.2.1]-oct-5-yl carboxylate (EP 287 356, Example 7) (2g, 10.9mmol) and lithium aluminium hydride (0.83g, 21.9mmol). This afforded the **title compound** as a clear gum (1.24g, 80%) b.p. 150°C, 0.7mm Hg (Kugelröhr).

Preparation 4
(±) 5-(2-Hydroxyethyl)-1-azabicyclo[3.2.1]octane

The title compound was prepared in a similar manner to Preparation 2 from (±) 5-methoxycarbonylmethyl-1-azabicyclo[3.2.1]octane (EP 363085, Description 11) (0.74g, 4.0 mmol) and lithium aluminium hydride (0.46g, 12.1 mmol). This afforded the **title compound** as a clear oil (0.54g, 87%) b.p. 200°C, 0.2 mm Hg (Kugelrohr)

^{1}H Nmr ($CDCl_3$) δ: 1.37-1.82 (8H, m, overlapping signals), 2.43-3.05 (6H, m, overlapping signals), 3.68 (2H, t, J=7Hz)

Preparation 5
4-Hydroxymethyl-1-azabicyclo[2.2.1]heptane

The title compound was prepared in a similar manner to Preparation 2 from methyl 1-azabicyclo[2.2.1]hept-4-yl carboxylate (B.S. Orlek et al., J. Med. Chem., 1991, 34, 2726) (3.13g, 20.2 mmol) and lithium aluminium hydride (1.92g, 50.6 mmol). This afforded the **title compound** as a colourless solid (1.76g, 69%) b.p. 250°C, 0.3 mmHg (Kugelrohr).

^{1}H Nmr ($CDCl_3$) δ: 1.27 (2H, m), 1.65 (2H, m), 2.32 (2H, s), 2.62 (2H, m), 2.94 (2H, m), 3.72 (1H, br s), 3.87 (2H, s)

Preparation 6
1-Benzyl-4-hydroxymethyl-4-hydroxypiperidine

To a suspension of sodium hydride (4.76g of an 80% dispersion in mineral oil, 0.159 mol) in dry dimethyl sulphoxide was added trimethyl sulphoxonium iodide (34.92g, 0.159 mol) over 1.5h. The mixture was stirred for 1h, then cooled in ice and treated with a solution of 1-benzyl-4-piperidone (25g, 0.132 mol) in dry dimethyl sulphoxide (25 ml). The reaction was allowed to warm to room temperature and stirred for a further 1h. The mixture was

diluted with water (500 ml) and extracted into diethyl ether (3x250 ml). The combined organic extracts were washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was extracted into pentane and purified by distillation to give a clear oil (22.48g) b.p. 175°C, 0.1 mm Hg (Kugelrohr). A solution of this epoxide in formic acid (100 ml) was stirred at room temperature overnight, then concentrated *in vacuo*. The residue was dissolved in methanol (200 ml), treated with a solution of sodium bicarbonate (30g) in water (100 ml) and stirred at room temperature for 21h. The reaction was concentrated to approximately one third the original volume, saturated with potassium carbonate, and extracted exhaustively with chloroform. The combined extracts were dried over sodium sulphate and concentrated *in vacuo* to give the **title compound** (24.5 g).

Preparation 7

1-Benzyl-1-azoniabicyclo[2.2.1]heptan-4-ol p-toluenesulphonate

A solution of 1-benzyl-4-hydroxymethyl-4-hydroxypiperidine (16.8g, 0.076 mol) in pyridine (150 ml) at 0°C was treated portionwise over 10 min with p-toluenesulphonyl chloride (14.86g, 0.078 mol) and the resulting solution was stored overnight at 8°C. The reaction was concentrated *in vacuo* and the residual oil was dissolved in chloroform and washed with saturated aqueous potassium carbonate. After drying over sodium sulphate the solution was concentrated *in vacuo*. The residual oil was dissolved in dry toluene and heated under reflux for 1.5h. The product was isolated by filtration and washed with diethyl ether to give the **title compound** as a beige solid (23.3g, 81%)

Preparation 8

4-Hydroxy-1-azabicyclo[2.2.1]heptane

A solution of 1-benzyl-1-azoniabicyclo[2.2.1]heptan-4-ol p-toluenesulphonate (5.0 g, 13.3 mmol) in ethanol (100 ml) was hydrogenated over 10% Pd-C (1.0 g) at atmospheric pressure for 18h. The catalyst was removed by filtration through kieselguhr, and the filtrate was concentrated *in vacuo*. The residue was partitioned between saturated aqueous potassium carbonate (20 ml) and chloroform (25 ml) and the aqueous layer was extracted exhaustively with chloroform. The combined organic extracts were dried over sodium sulphate, concentrated *in vacuo* and distilled to give the **title compound** as a colourless solid (1.2g, 80%), b.p. 175°C (kugelrohr).

^{1}H Nmr $CDCl_3$) δ: 1.58 (2H, m), 1.78 (2H, m), 2.37 (2H, s), 2.75 (2H, m), 3.17 (2H, m), 3.65 (1H, br s).

Preparation 9
3-(4-Benzyloxyphenyl)-1-propanol

A solution of 3-(4-hydroxyphenyl)-1-propanol (2.5g, 16.4 mmol) in acetone (40 ml) containing potassium carbonate (5.9g, 42.75 mmol) was treated with benzyl bromide (2.54 ml, 21.35 mmol) and refluxed for 3h. The mixture was concentrated *in vacuo* and partitioned between water (50 ml) and chloroform (50 ml). The aqueous phase was further extracted with chloroform (2x50 ml) and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. Purification by chromatography on silica using 0-8% methanol in chloroform as eluant afforded the **title compound** as a colourless solid (3.92g, 99%).

^{1}H Nmr ($CDCl_3$) δ: 1.36 (1H, s), 1.85 (2H, m), 2.63 (2H, t, J=7Hz), 3.65 (2H, t, J=7Hz), 5.04 (2H, s), 6.91 (2H, d, J=8Hz), 7.11 (2H, d, J=8Hz), 7.27-7.50 (5H, m).

Preparation 10
3-(4-Benzyloxyphenyl)propyl p-toluenesulphonate

A solution of 3-(4-benzyloxyphenyl)-1-propanol (4.15g, 17.1 mmol) in absolute chloroform (30 ml) was cooled in ice and treated with pyridine (3.92 ml, 48.5 mmol) followed by p-toluenesulphonyl chloride (6.16g, 32.3 mmol). The mixture was allowed to warm slowly to room temperature and left overnight. After dilution with diethyl ether (90 ml) the solution was washed with 1M orthophosphoric acid (50 ml) followed by saturated aqueous potassium hydrogen carbonate (50 ml) and water (50 ml). The organic phase was dried over sodium sulphate and then purified by chromatography on silica using 0-8% methanol in chloroform as eluant to give the **title compound** as a colourless solid (5.1g, 75%).

^{1}H Nmr ($CDCl_3$) δ: 1.92 (2H, q, J=7Hz), 2.45 (3H, s), 2.57 (2H, t, J=7Hz), 4.01 (2H, t, J=7Hz), 5.02 (2H, s), 6.83 (2H, d, J=8Hz), 6.97 (2H, d, J=8Hz), 7.30-7.47 (7H, m), 7.78 (2H, d, J=8Hz).

Preparation 11
4-(4-Phenoxyphenyl)butyl bromide

To a stirred suspension of aluminium chloride (13.33g, 0.1 mol) in dry dichloromethane (200 ml) was added dropwise over 0.5h 4-bromobutyryl chloride (11.6 ml, 0.1 mol). The resulting mixture was filtered and then added to a solution of diphenyl ether (25.5 g, 0.15

mol) in dry dichloromethane (150 ml) over 0.5 h. The mixture was stirred overnight and then treated with triethylsilane (48 ml, 0.3 mol). After 2 h the reaction was quenched with ice-water. The organic phase was washed with water (200 ml) followed by brine (2x100 ml) then dried over sodium sulphate and concentrated *in vacuo*. The residue was chromatographed on silica gel using 0-15% diethyl ether in 40-60 petroleum ether as eluant. Subsequent distillation afforded the **title compound** as a clear oil (22.12g, 73%) b.p. 146-160°C at 0.1 mm Hg.

^{1}H Nmr ($CDCl_3$) δ: 1.68-2.00 (4H, m, overlapping signals), 2.60 (2H, t, J=7Hz), 3.42 (2H, t, J=7Hz), 6.86-7.40 (9H, m).

Preparation 12

5-(4-Phenoxyphenyl)pentyl bromide

The title compound was prepared in a similar manner to Preparation 11 from 5-bromovaleryl chloride (13.39 ml, 0.1 mol), aluminum chloride (13.33g, 0.1 mol), diphenyl ether (25.5g, 0.15mol) and triethylsilane (48 ml, 0.3 mol). This afforded the **title compound** as a clear oil (17.56g, 55%) b.p. 165-180°C at 0.2 mm Hg.

^{1}H Nmr ($CDCl_3$) δ: 1.36-1.75 (4H, m, overlapping signals), 1.88 (2H, m), 2.60 (2H, t, J=7Hz), 3.40 (2H, t, J=7Hz), 6.86-7.38 (9H, m).

Preparation 13

5-(4-Hydroxyphenyl)-1-pentanol

A solution of 4-benzyloxybenzaldehyde (5.0g, 23.56 mmol) and triethyl 4-phosphono-crotonate (7.07g, 28.25 mmol) in dry tetrahydrofuran (50 ml) was added dropwise to a stirred ice cold slurry of sodium hydride (0.78g of an 80% dispersion in mineral oil, 26.0 mmol) in dry tetrahydrofuran (50 ml) containing 15-crown-5 (0.18g). The mixture was allowed to warm to room temperature. After 1h the reaction was quenched with glacial acetic acid (5ml) and concentrated *in vacuo*. The residue was partitioned between water (50 ml) and chloroform (100 ml). The aqueous layer was further extracted with chloroform (2x50 ml) and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. Crystallisation from ethyl acetate-pentane afforded a pale yellow solid (5.77g) which was dissolved in ethanol (100 ml) and hydrogenated at atmospheric pressure over 10% Pd-C (1g). After 3 h the reaction mixture was filtered through kieselgühr and then concentrated *in vacuo* to give ethyl 5-(4-hydroxyphenyl)pentanoate as a clear oil (4.08g). A solution of this ester in dry diethyl

ether (10ml) was added dropwise to a stirred suspension of lithium aluminum hydride (2.08g, 54.8 mmol) in dry diethyl ether (150 ml). After 2.5h the reaction was quenched with wet diethyl ether followed by a minimum amount of water. The reaction was filtered, and the precipitate was washed with methanol. The combined filtrate and washings were concentrated *in vacuo*. The residue was dissolved in water, acidified with 5M hydrochloric acid, saturated with sodium chloride and extracted exhaustively with chloroform. The combined chloroform extracts were dried over sodium sulphate and concentrated *in vacuo* to give the **title compound** as a colourless solid. The precipitate was dissolved in 5M hydrochloric acid, and the solution was saturated with sodium chloride and filtered through kieselguhr. Exhaustive extraction with chloroform yielded additional product, bringing the total recovery of the **title compound** to 3.04g (92%).

^{1}H Nmr ($CDCl_3$) δ: 1.25 -1.80 (7H, m, overlapping signals), 2.52 (2H, t, J=7Hz), 3.62 (2H, t, J=7Hz), 4.90 (1H, br s), 6.74 (2H, d, J=8Hz), 7.02 (2H, d, J=8Hz).

Preparation 14

5-(4-Benzyloxyphenyl)-1-pentanol

A solution of 5-(4-hydroxyphenyl)-1-pentanol (3.04g, 16.98 mmol) in ethanol (40 ml) containing potassium carbonate (6.1g, 44.2 mmol) was treated with benzyl bromide (2.63ml, 22.07 mmol) and refluxed for 1h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (50 ml) and chloroform (50 ml). The aqueous phase was further extracted with chloroform (2x50 ml) and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. Purification by chromatography on silica using 0-8% methanol in chloroform as eluant afforded the **title compound** as a colourless solid (4.31g, 94%)

^{1}H Nmr ($CDCl_3$)δ: 1.15-1.70 (7H, m, overlapping signals), 2.55 (2H, t, J=7Hz), 3.62 (2H, t, J=7Hz), 5.01 (2H, s), 6.87 (2H, d, J=8Hz), 7.07 (2H, d, J=7Hz), 7.23-7.50 (5H, m).

Preparation 15

5-(4-Benzyloxyphenyl)pentyl p-toluenesulphonate

The title compound was obtained using the procedure described in Preparation 10 from 5-(4-benzyloxyphenyl)-1-pentanol (3.3g, 12.2 mmol), pyridine (3.0 ml, 37.2 mmol) and p-toluenesulphonyl chloride (4.66g, 24.4 mmol). After a reaction time of 4h at room

temperature the mixture was worked up as previously described to give the title compound as a colourless solid (3.64 g, 70%).

^{1}H Nmr ($CDCl_3$) δ: 1.20-1.76 (6H, m, overlapping signals), 2.33-2.60 (5H, m, overlapping signals), 4.0 (2H, t, J=6Hz), 5.0 (2H, s), 6.83 (2H, d, J=8Hz), 7.02 (2H, d, J=8Hz), 7.23-7.50 (7H, m), 7.77 (2H, d, J=8Hz).

Example 1

4-[2-(3,4-Dichlorophenoxy)ethyl]-1-azabicyclo[2.2.1]heptane hydrochloride (E1)

A solution of 4-(2-hydroxyethyl)-1-azabicyclo[2.2.1]heptane (0.5g, 3.55mmol) in dry tetrahydrofuran (40ml), under nitrogen, was treated with 3,4-dichlorophenol (0.87g, 5.32mmol) in dry tetrahydrofuran (2ml), followed by triphenylphosphine (1.21g, 4.61mmol) in tetrahydrofuran (2ml). Diethyl azodicarboxylate (0.80g, 4.61mmol) was added to the reaction over 0.5h and the mixture was stirred overnight at room temperature. The reaction was concentrated *in vacuo*, treated with saturated aqueous potassium carbonate (25ml) then extracted into chloroform (3x25 ml). The combined organic extracts were dried over sodium sulphate, concentrated *in vacuo* and the residue chromatographed on neutral alumina in a gradient of 0-2% methanol in chloroform. The gum produced was converted into the HCl salt, which was washed thoroughly with diethyl ether then crystallised to afford the **title compound** as a white solid (0.65g), m.p. 188-190°C (methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.70-2.09 (4H, m), 2.18 (2H, t, J=7Hz), 3.12 (2H, s), 3.23-3.56 (4H, m), 4.20 (2H, t, J=7Hz), 7.06 (1H, dd, J=3, 10Hz), 7.35 (1H, d, J=3Hz). 7.62 (1H, d, J=10Hz).

Example 2

4-[2-(4-Benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.1]heptane hydrochloride (E2)

The title compound was prepared in a similar manner to Example 1 from 4-(2-hydroxyethyl)-1-azabicyclo[2.2.1]heptane (0.5g, 3.55mmol), 4-benzyloxyphenol (1.06g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.80g, 4.61mmol). This afforded the **title compound** as a white solid (0.24g), m.p. 209-212°C (from methanol-diethyl ether.

^{1}H Nmr (DMSO-d_6) δ: 1.70-2.09 (4H, m), 2.16 (2H, t,(J=6Hz), 3.13 (2H, s), 3.23-3.66 (4H, m), 4.10 (2H, t, J=6Hz), 5.12 (2H, s), 6.89-7.08 (4H, m), 7.36-7.57 (5H, m).

Example 3

4-[2-(2-Dibenzofuranyloxy)ethyl]-1-azabicyclo[2.2.1]heptane hydrochloride (E3)

The title compound was prepared in a similar manner to Example 1 from 4-(2-hydroxyethyl)-1-azabicyclo[2.2.1]heptane (0.39g, 2.77mmol), 2-hydroxydibenzofuran (0.76g, 4.15mmol), triphenylphosphine (0.94g, 3.60mmol) and diethyl azodicarboxylate (0.63g, 3.60mmol). The crude product was chromatographed on silica in a gradient of 5-20% methanol in chlorofrom. Pooling of fractions containing the major slower running component afforded an oil which was treated with ethereal hydrogen chloride to give the **title compound** as a white solid (0.12g), m.p 206-209°C (from methanol/acetone/diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.75-2.13 (4H, m), 2.26 (2H, t, J=6Hz), 3.20 (2H, s), 3.26-3.57 (4H, m), 4.30 (2H, d, J=6Hz), 7.19 (1H, dd, J=2, 7Hz), 7.40-7.79 (5H, m), 8.22 (1H, d, J=7Hz).

Example 4

(±)5-(4-Benzyloxyphenoxymethyl)-1-azabicyclo[3.2.1]octane hydrochloride (E4)

The title compound was prepared in a similar manner to Example 1 from (±)5-hydroxymethyl-1-azabicyclo[3.2.1]octane (0.5g, 3.55mmol), 4-benzyloxyphenol (1.065g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) diethyl azodicarboxylate (0.80g, 4.61mmol). This afforded the **title compound** as a white solid (0.11g), m.p. 188-191°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.48-1.55 (1H, m), 1.60-1.97 (5H, m), 3.02-3.16 (4H, m), 3.25-3.37 (2H, m), 3.80 (2H, s), 4.95 (2H, s), 6.74-6.98 (4H, m), 7.18-7.35 (5H, m).

Example 5

(±)5-(4-Benzylphenoxymethyl)-1-azabicyclo[3.2.1]octane hydrochloride (E5)

The title compound was prepared in a similar manner to Example 1 from (±)5-hydroxymethyl-1-azabicyclo[3.2.1]octane (0.5g, 3.55mmol), 4-hydroxydiphenylmethane (0.98g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.80g, 4.61mmol). This afforded the **title compound** as a white solid (0.15g), m.p. 168°C (dec) (from methanol-ether).

^{1}H Nmr (DMSO-d_6) δ: 1.62-1.70 (1H, m), 1.74-2.11 (5H, m), 3.16-3.30 (4H, m), 3.38-3.51 (2H, m), 3.92 (2H, s), 3.97 (2H, s) 6.88-6.93 (2H, m), 7.14-7.25 (5H, m), 7.27-7.34 (2H, m).

Example 6

(±)5-(2-Dibenzofuranyloxy)methyl-1-azabicyclo[3.2.1]octane hydrochloride (E6)

The title compound was prepared in a similar manner to Example 1 from (±)5-hydroxymethyl-1-azabicyclo[3.2.1]octane (0.53g, 3.76mmol), 2-hydroxydibenzofuran (1.04g, 5.64mmol) triphenylphosphine (1.28g, 4.89mmol) and diethyl azodicarboxylate (0.85g, 4.89mmol). The crude product was chromatographed on neutral alumina in a gradient of 0.5-2% methanol in toluene. Pooling of fractions containing the faster running component and conversion of the resulting gum into the hydrochloride salt afforded the title compound as a white solid (0.98g), m.p. 224-225°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.62-2.22 (6H, m), 3.15-3.59 (6H, m), 4.10 (2H, s), 7.08-7.17 (1H, m), 7.33-7.87 (5H, m), 8.09-8.18 (1H, m).

Example 7

(±) 5-[2-(2-Dibenzofuranyloxy)ethyl]-1-azabicyclo[3.2.1]octane hydrochloride (E7)

The title compound was prepared in a similar manner to Example 1 from (±) 5-(2-hydroxyethyl)-1-azabicyclo[3.2.1]octane (0.53g, 3.42 mmol), 2-hydroxydibenzofuran (0.95g, 5.13 mmol), triphenylphosphine (1.17g, 4.45 mmol) and diethyl azodicarboxylate (0.54ml, 3.42 mmol) employing a reaction time of 2h. The crude product was purified by chromatography on neutral alumina using 0.5-2% methanol in toluene as eluant, and converted into the hydrochloride salt to give the title compound as a coulourless solid (0.7g), m.p. 137-138°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.60-2.08 (8H, m), 3.10-3.50 (6H, m), 4.14 (2H, t, J=5Hz), 7.12, (1H, dd, J=8Hz and 2Hz), 7.40 (1H, t, J=8Hz), 7.52 (1H, t, J=8Hz), 7.63 (1H, d, J=8Hz), 7.67 (1H, d, J=8Hz), 7.77 (1H, d, J=2Hz), 8.14 (1H, d, J=8Hz), 10.93 (1H, br s).

Example 8

4-[2-(4-Phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.1]heptane hydrochloride (E8)

The title compound was prepared in a similar manner to Example 1 from 4-(2-hydroxyethyl)-1-azabicyclo[2.2.1]heptane (0.62g, 4.4 mmol), 4-phenoxyphenol (1.23g, 6.61 mmol), triphenylphosphine (1.5g, 5.72 mmol) and diethyl azodicarboxylate (0.9 ml, 5.72 mmol). The reaction mixture was concentrated *in vacuo*, and the residue was converted into the hydrochloride salt with ethereal hydrogen chloride. After trituration with ether, the salt was treated with saturated aqueous potassium carbonate (20 ml) and extracted into chloroform (3x25 ml). The combined extracts were dried over sodium sulphate, concentrated *in vacuo* and then purified on neutral alumina using 0-2% methanol in chloroform as eluant. After pooling pure fractions the product was treated with ethereal hydrogen chloride to give the **title compound** as a colourless solid (0.85g), m.p. 209-211°C (methanol - acetone - diethyl ether)

^{1}H Nmr (DMSO-d_6) δ: 1.73 (2H, m), 1.93 (2H, m), 2.12 (2H, t, J=6Hz), 3.07 (2H, s), 3.25 (4H, m), 4.12 (2H, t, J=6Hz), 6.88-7.13 (7H, m), 7.38 (2H, t, J=7Hz).

Example 9

4-[3-(4-Benzyloxyphenyl)propyloxymethyl]-1-azabicylo[2.2.1]heptane hydrochloride (E9)

A solution of 4-hydroxymethyl-1-azabicyclo[2.2.1]heptane (0.2g, 1.57 mmol) in dry N,N-dimethylformamide (5ml) was treated with sodium hydride (50mg of an 80% dispersion in mineral oil, 1.66 mmol) and the mixture was stirred at 50°C under nitrogen until hydrogen evolution had ceased. Portionwise addition of 3-(4-benzyloxyphenyl)propyl p-toluenesulphonate (0.58g, 1.57 mmol) was carried out over 1h, and the mixture was stirred for a further 1h. The reaction was concentrated *in vacuo* and the residue was co-evaporated with successive portions of toluene. The residue was treated with saturated aqueous postassium carbonate (10ml) and extracted into chloroform (3x15 ml). The combined extracts were dried over sodium sulphate and then concentrated *in vacuo*. The crude product was purified by flash chromatography on neutral alumina using 0-15% methanol in chloroform as eluant. Pooled fractions containing the faster running component were converted into the hydrogen chloride salt to give the **title compound** as a colourless solid (0.11g), m.p. 166-168°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.72 (2H, m), 1.87(2H, m), 2.03 (2H, m), 2.65 (2H, t, J=8Hz), 3.12 (2H, s), 3.28-3.55 (6H, m, overlapping signals), 3.68 (2H, s), 5.16 (2H, s), 7.01 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz), 7.37-7.63 (5H, m).

Example 10

4-[5-(4-Phenoxyphenyl)pentyloxy]-1-azabicyclo[2.2.1]heptane hydrochloride (E10)

A solution of 1-benzyl-1-azoniabicyclo[2.2.1]heptan-4-ol p-toluenesulphonate (0.5g, 1.33 mmol) in dry N,N-dimethylformamide (7ml) was treated with sodium hydride (80 mg of an 80% dispersion in mineral oil, 2.66 mmol) and then stirred under nitrogen at room temperature for 1h. A solution of 5-(4-phenoxyphenyl)pentyl bromide (0.85g, 2.66 mmol) in dry N, N-dimethylformamide (2ml) was added, and the mixture was stirred for 3h. The reaction was quenched with glacial acetic acid (0.5ml) and then concentrated *in vacuo*. After co-evaporation with successive portions of toluene, the residue was disolved in ethanol (10 ml) and hydrogenated at atmospheric pressure over 10% Pd-C (0.1g) for 2h. The reaction mixture was filtered through a pad of kieselguhr and the filtrate was concentrated *in vacuo*. The residue was treated with saturated aqueous potassium carbonate (20 ml) and extracted into chloroform (3x20ml). The combined extracts were dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography on neutral alumina using 0-15% methanol in chloroform as eluant. After pooling pure fractions the product was treated with ethereal hydrogen chloride to give the title compound as a colourless solid (0.14g), m.p. 129-131°C (from acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.33 (2H, m), 1.55 (4H, m), 1.80-2.10 (4H, m), 2.53 (2H, t, J=7Hz), 3.18 (2H, s), 3.30-3.58 (6H, m, overlapping signals), 6.93 (4H, m), 7.11(1H, t, J=8Hz), 7.22 (1H, d, J=8Hz), 7.38 (2H, t, J=8Hz).

Example 11

4-(4-Benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride (E11)

The title compound was prepared in a similar manner to Example 1 from 4-hydroxymethyl-1-azabicyclo[2.2.1]heptane (0.5g, 3.94 mmol), 4-benzyloxyphenol (1.18g, 5.91 mmol), triphenylphosphine (1.55g, 5.91 mmol) and diethyl azodicarboxylate (0.93ml, 5.91 mmol). After a reaction period of 5h the mixture was worked up as previously described for Example 1. Purification on neutral alumina using 5% ethanol in chloroform

as eluant afforded a pale yellow oil which was treated with ethereal hydrogen chloride to give the **title compound** as a colourless solid (0.09g), m.p. 206-208°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.73 (2H, m), 2.02 (2H, m), 3.12 (2H, s), 3.20-3.50 (4H, m, overlapping signals), 4.17 (2H, s), 5.03 (2H, s), 6.93 (4H, m), 7.26-7.48 (5H, m).

Example 12

4-[4-(4-Phenoxyphenyl)butyloxy]-1-azabicyclo[2.2.1]heptane hydrochloride (E12)

The title compound was prepared in a similar manner to Example 10 from 1-benzyl-1-azoniabicyclo[2.2.1]heptan-4-ol p-toluenesuphonate (0.5g, 1.33 mmol), sodium hydride (80 mg of an 80% dispersion in mineral oil, 2.66 mmol) and 4-(4-phenoxyphenyl)butyl bromide (0.89g, 2.91 mmol). The crude product was purified by chromatography on silica using 5-10% ethanol in chloroform as eluant, and treated with ethereal hydrogen chloride to give the **title compound** as a colourless solid m.p. 115-117.5°C (from acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.46-1.67 (4H, m), 1.85-2.06 (4H, m), 2.57 (2H, t, J=7Hz), 3.17 (2H, s), 3.30-3.60 (6H, m, overlapping signals), 6.93 (4H, m, overlapping signals), 7.11 (1H, t, J=7Hz), 7.21 (2H, d, J=8Hz), 7.38 (2H, t, J=8Hz).

Example 13

4-[3-(4-Benzyloxyphenyl)propyloxy]-1-azabicyclo[2.2.1]heptane hydrochloride (E13)

A solution of 4-hydroxy-1-azabicylo[2.2.1]heptane (0.38g, 3.36 mmol) in dry N, N-dimethylformamide (15ml) was treated under nitrogen with sodium hydride (120 mg of an 80% dispersion in mineral oil, 4.0 mmol). The mixture was warmed to 40-50°C and stirred for 2h. The temperature was raised to 60°C and a solution of 3-(4-benzyloxyphenyl)propyl tosylate (0.90g, 2.69 mmol) in dry N, N-dimethylformamide (8ml) was added dropwise over 2h. After a further 1h at 60°C the reaction was cooled and quenched with glacial acetic acid (0.23 ml). The reaction was concentrated *in vacuo* and then partitioned between chloroform (20 ml) and saturated aqueous potassium carbonate (20 ml). The aqueous phase was extracted with chloroform (2x20 ml) and the combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. Purification on neutral alumina using 1-2% ethanol in chloroform as eluant afforded a colourless

crystalline solid which was treated with ethereal hydrogen chloride to give the **title compound** as a colourless solid (0.30g) m.p. 180-181°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.78 (2H, m); 1.92 (2H, m); 2.02 (2H, m); 2.56 (2H, t, J= 7Hz); 3.18 (2H, s); 3.25-3.60 (6H, m); 5.07 (2H, s), 6.92 (2H, d, J=8Hz); 7.12 (2H, d, J=8Hz); 7.28-7.50 (5H, m).

Example 14

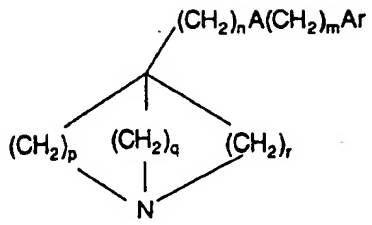
4-[5-(4-Benzyloxyphenyl)pentyloxy]-1-azabicyclo[2.2.1]heptane hydrochloride (E14)

A solution of 4-hydroxy-1-azabicyclo [2.2.1] heptane (0.38g, 3.36 mmol) in dry N, N-dimethylformamide (15ml) was treated under nitrogen with sodium hydride (120mg of an 80% dispersion in mineral oil, 4.0 mmol). The mixture was warmed to 50°C and stirred for 2h. The temperature was raised to 60°C and a solution of 5-(4-benzyloxyphenyl) pentyl p-toluenesulphonate (1.07g, 2.52 mmol) in dry N, N-dimethylformamide (9ml) was added dropwise over a period of 3h. After a further 45min at 60°C the mixture was cooled and quenched with glacial acetic acid (0.23ml). The reaction was concentrated *in vacuo* then partitioned between chloroform (75ml) and saturated aqueous potassium carbonate (75ml). The aqueous phase was exhaustively extracted with chloroform. The combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. Purification on neutral alumina using 1% ethanol in chloroform as eluant followed by treatment with ethereal hydrogen chloride afforded the **title compound** as a colourless solid (0.30g) m.p. 150-151.5°C (acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.32 (2H, m); 1.53 (4H, m); 1.82-2.08 (4H, m); 2.50 (2H, t, J=7Hz), 3.17 (2H, s); 3.25-3.60 (6H, m); 5.06 (2H, s); 6.92 (2H, d, J=8Hz), 7.10 (2H, d, J=8Hz); 7.28-7.50 (5H, m).

Claims :

1. A compound of formula (I):



Formula (I)

in which

p, q and r each independently represent an integer from 1 to 4;
n is 0 to 6;
m is 0 to 6;
A is a bond, -CH=CH-, -C≡C-, oxygen, sulphur or NR^1;
R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl; and
Ar is aryl or heteroaryl, each of which may be optionally substituted;

or a salt thereof.

2. A compound according to claim 1 wherein p and r are independently 2 or 3.

3. A compound according to claim 1 or claim 2 wherein q is 1 or 2.

4. A compound according to any of claims 1 to 3 wherein A is oxygen or a bond.

5. A compound according to any of claims 1 to 4 wherein the length of the chain $-(CH_2)_nA(CH_2)_m$ is from 2 to 6 atoms.

6. A compound according to any of claims 1 to 5 wherein m is 0 to 3.

7. A compound according to claim 1, selected from :

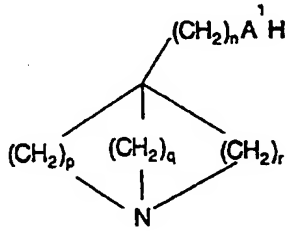
4-[2-(3,4-dichlorophenoxy)ethyl]-1-azabicyclo[2.2.1]heptane,

4-[2-(4-benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.1]heptane,
4-[2-(2-dibenzofuranyloxy)ethyl]-1-azabicyclo[2.2.1]heptane,
(±)5-(4-benzyloxyphenoxymethyl)-1-azabicyclo[3.2.1]octane,
(±)5-(4-benzylphenoxymethyl)-1-azabicyclo[3.2.1]octane,
(±)5-(2-dibenzofuranyloxy)methyl-1-azabicyclo[3.2.1]octane;
(±) 5-[2-(2-dibenzofuranyloxy)ethyl]-1-azabicyclo[3.2.1]octane,
4-[2-(4-phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.1]heptane,
4-[3-(4-benzyloxyphenyl)propyloxymethyl]-1-azabicylo[2.2.1]heptane,
4-[5-(4-phenoxyphenyl)pentyloxy]-1-azabicyclo[2.2.1]heptane,
4-(4-benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane,
4-[4-(4-phenoxyphenyl)butyloxy]-1-azabicyclo[2.2.1]heptane,
4-[3-(4-benzyloxyphenyl)propyloxy]-1-azabicyclo[2.2.1]heptane, and
4-[5-(4-benzyloxyphenyl)pentyloxy]-1-azabicyclo[2.2.1]heptane,

or a pharmaceutically acceptable salt thereof.

8. A process for the preparation of a compound of formula (I) as defined in any of claims 1 to 7 which comprises:

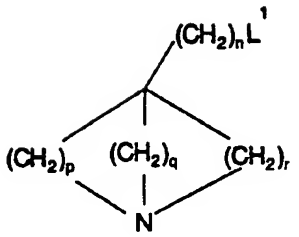
(a) for compounds of formula (I) in which A is O, S or NR^1, reaction of a compound of formula (II):



Formula (II)

in which p, q, r and n are as described for formula (I) and A^1 is O, S or NR^1, with a compound of formula $L(CH_2)_mAr$ in which m and Ar are as described for formula (I), and L is a leaving group;

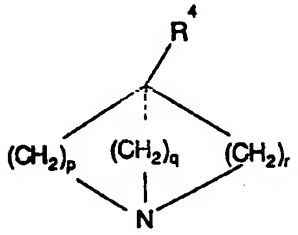
(b) for compounds of formula (I) in which A is O, S or NR^1, reaction of a compound of formula (III):



Formula (III)

in which p, q, r and n are as described for formula (I) and L^1 is a group displaceable by a nucleophile, with a compound of formula $HA^1(CH_2)_mAr$ where m and Ar are as described for formula (I) and A^1 is as described for formula (II); or

(c) for compounds of formula (I) in which A is NR^1, reduction of a compound of formula (IV) :



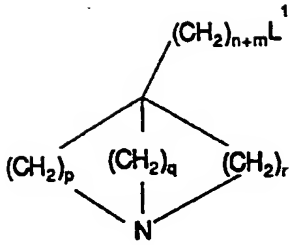
Formula (IV)

in which R^4 represents the group

$-(CH_2)_nN(R^1)C(O)(CH_2)_{m-1}Ar$ or $-(CH_2)_{n-1}C(O)N(R^1)(CH_2)_mAr$,

and p, q, r, n, m, and Ar are as described for formula (I);

(d) for compounds of formula (I) in which A is a bond, reaction of a compound of formula (V) :

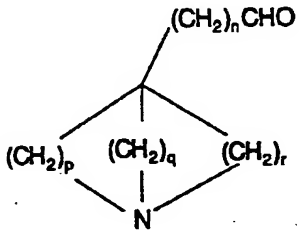


Formula (V)

(wherein L^1, p, q, r, m and n are as hereinbefore defined).

with a compound of formula X^1Ar in which Ar is as described for formula (I), and X^1 is an alkali metal;

(e) For compounds wherein A is -CH=CH- reaction of a compound of formula (VI) :



Formula (VI)

(wherein n, p, q and r are as hereinbefore defined) with a reagent serving to introduce the group Ar;

(f) Interconversion of one compound of formula (I) to a different compound of formula (I) e.g. the reduction of a compound wherein A is -CH=CH- to a compound wherein A is $-CH_2CH_2-$;
and optionally thereafter forming a salt.

9. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 7 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

10. A compound of formula (I) as defined in any of claims 1 to 7 or a pharmaceutically acceptable salt thereof for use in therapy.

11. A method of treatment of a condition or disease related to the accumulation of calcium in the brain cells of mammals which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

5

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00174

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/08; A61K31/395; C07D471/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	CHEMICAL ABSTRACTS, vol. 111, 1989, Columbus, Ohio, US; abstract no. 232473, A.G. ANDERSON ET AL. 'Synthesis of derivatives of 3-hydroxymethyl-3-phenylazetidine and attempted conversions to 3-phenyl-1-azabicyclo(1.1.1.)pentane or 3-phenyl-1-azabicyclo(2.1.1.)hexane.' page 757 ; see abstract * RN 123974-27-6 * & 'Gazz. Chim. Ital. 1989, 119(2), 81-5' --- -/--	1,4,6

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 MAY 1993	-8. 06. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL ABSTRACTS, vol. 84, 1976, Columbus, Ohio, US; abstract no. 121623y, H. BOCHOW ET AL. '4-Phenyl-2-chinuclidinol' see abstract * RN 58664-89-4 , RN 51069-11-5 * & 'Chem. Ber. 1975,108(11), 3475-82' ---	1,4,6
X	CHEMICAL ABSTRACTS, vol. 93, 1980, Columbus, Ohio, US; abstract no. 70664p, C.A. GROB ET AL. 'A reexamination of inductive substituent constants derived from pKa values of 4-substituted quinuclidines. Polar effects. Part VIII.' page 884 ; see abstract * RN 51069-12-6 * & 'Helv. Chim. ACta 1980, 63(1),57-62' ---	1,4,6
X	CHEMICAL ABSTRACTS, vol. 71, 1969, Columbus, Ohio, US; abstract no. 22026f, E.E. MIKHLINA ET AL. 'Synthesis of 4-aminoquinuclidine and its derivatives.' see abstract * RN 22778-75-2 * & 'Khim. Geterosikl. Soedin. 1969,(2), 278-80' ---	1
X	WO,A,9 113 885 (BEECHAM GROUP PLC) 19 September 1991 see claims ---	1,9
X	DE,A,2 009 555 (SOGERAS) 8 October 1970 see claims -----	1,9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300174
SA 70178

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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DE-A-2009555	08-10-70	AT-A-	294114	15-10-71
		BE-A-	746034	31-07-70
		CH-A-	502378	31-01-71
		FR-A,B	2034605	11-12-70
		GB-A-	1250534	20-10-71
		NL-A-	7003014	07-09-70
		SE-B-	377803	28-07-75
		US-A-	3987042	19-10-76

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